

THE IMPORTANCE AND FUTURE OF MALARIA RESEARCH IN AFRICA

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MALARIA: A DEVELOPMENT PROBLEM IN AFRICA

Malaria is a major threat to public health and economic development in Africa. Current estimates indicate that at least one to three million children die of malaria each year in Africa alone. Efforts to eradicate malaria have failed and parasite resistance to the most commonly used and affordable anti-malarial drugs is developing rapidly. Insecticide resistance in the vector is also an evolving problem. A malaria vaccine is the subject of much research but its testing is incomplete and full deployment remains a distant goal.

MALARIA RESEARCH IN AFRICA

The goals of malaria control may never be achieved without strong involvement of those scientists who are directly affected by this terrible disease in their daily life. Until recently, true participation of African scientists in the international effort to control malaria has been minimal. The need for strong African research institutions and highly trained African malariologists was highlighted at the Dakar meeting of 1997 that led to the launch of the Multilateral Initiative on Malaria (MIM). Since 1998, when the MIM began, the number of on-going MIM/TDR UNICEF/UNDP/World Bank/World Health Organization Special Program for Research & Training in Tropical Diseases (TDR) projects involving African Institutions and African scientists as principal investigators have increased sharply. Basic research provides the critical scientific base for the development of intervention tools (drugs, insecticides, vaccines, and diagnostics) for malarial control in Africa. For example, the study of phospholipid metabolism in general and phosphatidylcholine synthesis in particular has provided information resulting in the identification of novel and potent antimalarial compounds. Promising models for the use of molecular markers of antimalarial resistance as novel tools for the surveillance of drug resistance in malaria endemic countries are being developed and updated.¹⁻³ As a result of the availability of the completely sequenced malaria genome, novel biochemical drug targets unique to malaria parasites have been discovered (e.g., apicoplast enzymes)⁴ and new compounds have entered clinical trials. The investigations of human and parasite gene polymorphisms related to the pathogenesis of severe malaria in children with different genetic backgrounds, in ethnic groups⁵ and with hemoglobinopathies^{6,7} conducted in different sites in Africa have provided morbidity and mortality data that can be used by national and local decision makers as prognostic markers and for guidance in patient management. Nevertheless, translation of the findings on human and/or parasite genes to immediate interventions in the field remains a big challenge.

NETWORKING FOR MORE AND BETTER DATA

Although strong collaborations with some northern research institutions were established prior to the MIM, there was little communication between the different African researchers. This resulted in the generation of often incomplete or conflicting findings. It was obvious that the creation of research networks of scientists focusing on similar or related questions filled a great need. Major networks include Antimalarial Drug Resistance Network (ADRN), Severe Malaria in African Children (SMAC), Paludisme+ (Pal+), Malaria Immunology and Pathogenesis Consortium (MIMPAC), Pregnancy-Associated Malaria Vaccines (PAMVAC), African Malaria Network Trust (AMANET), and INDEPTH, an international network of field sites with continuous demographic evaluation of populations and their health in developing countries. These networks are investigating antimalarial drug resistance, malaria immunology, pathogenesis, entomology, and developing clinical trials to assess new and improved tools. Common themes of these networks are training in standardized protocols and methods, sharing data to ensure comparability of final results among various study sites and sharing of research capability and resources.

A better understanding of the acquisition of protection against disease caused by *Plasmodium falciparum* in children exposed to intense transmission is one of the key issues being explored by African researchers. This acquisition of protection is an evolving process that involves complex mechanisms, mediated by both immunologic and genetic (host and parasite) factors. The general objective of a collaborative MIM/TDR project carried out in Gabon and Congo with northern partners is to describe the influence of the sickle cell trait on the development of naturally acquired immunity in children living under high malaria transmission.⁶ The regional collaboration between research groups in Nigeria and the United Kingdom is based on the investigation of the humoral immune responses to merozoite surface protein 1 (MSP-1) (specifically, antibodies that inhibit MSP-1 secondary processing and blocking antibodies) in Nigerian residents.⁸ The MIM/TDR Antimalarial Drug Resistance Network (ADRN - <http://www.nlm.nih.gov/adrn/>) seeks to systematically define the characteristics of *P. falciparum* infections with parasites resistant to first-line⁹ and alternative antimalarial drugs in the participating sites and to strengthen the capability of the scientists and control managers to use data generated locally.

Speaking frankly, there is wholly inadequate dialogue between malaria researchers and malaria control program managers. The ideal situation would be for the malaria control manager to come up with a "shopping list" of national malaria control activities on which basic and applied research can be brought to bear. The scientist could then take up the challenge to come up with tools which can be used by the control program; an example would be developing high throughput field assays to monitor sulfadoxine-pyrimethamine resistance

and insecticide resistance based on novel malaria dihydrofolate reductase or mosquito cytochrome P450 alleles,¹⁰ respectively. Microarray technology is a basic research tool that can be applied directly to malaria control. The most cogent example is the development of DNA chips based on single nucleotide polymorphisms in antimalarial drug target genes for monitoring antimalarial drug resistance in the field. The linkage between researchers, clinicians, control workers, and policy makers is a quintessential element of malaria control.

WHAT IS THE FUTURE FOR MALARIA RESEARCH IN AFRICA?

It is both bright and bleak at the same time. There are new funding initiatives from many organizations. The European Union Framework Program 6 is promoting European leadership in malaria research through Networks of Excellence with a center of gravity in Europe, but the program maintains a North-South (INCO III) research component. The European and Developing Countries Clinical Trials Partnership (EDCTP) is an important initiative to sustain the African and European partnership through the development of vaccine and drug clinical trials. Unfortunately, only limited funds from industry are committed for research capacity building in Africa.

The availability of the genome data for *Homo sapiens*, *Plasmodium falciparum*, and *Anopheles gambiae* has ushered in a new exciting era in which postgenomics research approaches will be brought to bear on malaria. In the near future, fundamental knowledge and bioinformatics will be strengthened to allow the basic tools required for functional genomics studies to be developed in Africa. Collaborations based on blood collections in Africa linked to laboratory research in Europe and America is controversial. The long-term objective of African researchers is to develop high quality research in diversified topics of malaria in well-equipped and supported laboratories based in Africa and to be full members of the scientific community. These are indeed exciting times filled with challenges and opportunities. So why the pessimism?

Malaria research outside the MIM is fragmented in Africa; within MIM institutions, the Francophone/Anglophone divide still exists, linkages are weak and irregular, and the bulk of funding, even in these halcyon days, goes to the northern partners. Embracing postgenomics research (with the astronomical costs associated with establishing proteomics and microarray platforms) will remain a pipe dream for African researchers as long as the funding imbalance remains. Leadership in malaria in the north must exist in tandem with African excellence. There must be a meeting of minds between the northern and southern partners and those who hold the purse strings to improve funding for malaria research in Africa. True, the control of malaria is a long-term objective and the sharing of reagents, resources, and competencies are crucial to its achievement. Yet, the worst possible outcome in these propitious times, and unacceptable at anytime, would be for African malaria researchers to resign themselves to being conduits for field material for northern partners. A massive infusion of funds for capacity building, infrastructure development, and day-to-day research activities will not only dispel the pessimism, but will create an environment in which African and northern partners work side by side as equal intel-

lectual partners with a common goal: the control of malaria in Africa.

OPPORTUNITIES, CHALLENGES, AND EXPECTATIONS

There is hope on the horizon for the malaria research landscape if the current favorable funding climate for malaria results in more resources being made available for African malaria researchers. New initiatives such as the EDCTP are beacons of hope and offer great expectations for African scientists. Other funding agencies and initiatives must make the bold decision to channel more malaria dollars into Africa than they have done before; at the present time, millions are going to the north while the south receives only a trickle. There is hope if African malaria researchers become more adept not only in providing global leadership in malaria research and mentoring young African scientists for the next generation, but also in taking advantage of the current funding opportunities to propose bold new ground-breaking projects that are internationally competitive for long-term sustainability. There is great optimism that genomics research will result in new drugs, vaccines, diagnostics, and new tools for malaria vector control. There is hope if African scientists seize on the opportunities and challenges that the post-genomics era offers and become active participants in genomics research. Finally, there is optimism that close linkages between African malaria researchers and national malaria control programs will facilitate the translation of research findings into intervention tools for the control of malaria.

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